

Consensus statement

Hepatitis A booster vaccination: is there a need?

*P Van Damme, J Banatvala, O Fay, S Iwarson, B McMahon, K Van Herck, D Shouval, P Bonanni, B Connor, G Cooksley, G Leroux-Roels, F Von Sonnenburg, the International Consensus Group on Hepatitis A Virus Immunity**

Hepatitis A is one of the most common vaccine-preventable infectious diseases in the world. Effective vaccines against hepatitis A have been available since 1992, and they provide long-term immunity against the infection. However, there is no worldwide consensus on how long protection will last or whether there will be a need for hepatitis A virus (HAV) booster vaccinations in the future. In most countries, booster-vaccination policy is guided by manufacturers' recommendations, national authorities, or both. In June, 2002, a panel of international experts met to review the long-term immunogenicity and protection conferred by HAV vaccine in different population groups. Data have shown that after a full primary vaccination course, protective antibody amounts persist beyond 10 years in healthy individuals, and underlying immune memory provides protection far beyond the duration of anti-HAV antibodies. The group concluded that there is no evidence to lend support to HAV booster vaccination after a full primary vaccination course in a healthy individual. However, further investigations are needed before deciding if boosters can be omitted in special patient-groups.

About 1·4 million new cases of hepatitis A are reported worldwide every year, although the true incidence is thought to be up to ten times higher.^{1,2} Hepatitis A remains one of the most common vaccine-preventable infectious diseases among travellers to the developing world.³ Worldwide, the prevalence of hepatitis A virus (HAV) is highest in developing countries, where seroprevalence rates can reach 100% before the age of 10 years (figure).^{4,5} Rates in the industrialised world are low (ranging from 10% by mid-adolescence up to 70% in late adulthood),⁴ and have fallen over the past few decades, mainly because of improvements in socioeconomic conditions leading to improved hygiene and sanitation.⁶⁻⁹ As a result, an age-related shift in seroprevalence has taken place, in which large numbers of individuals are at risk of infection during adolescence and adulthood—eg, while travelling from areas of low endemicity to areas of high or intermediate endemicity. This age-related shift results in increased morbidity and mortality.¹⁰ Furthermore, imported hepatitis A—resulting from the migration of recently infected individuals from areas of high or intermediate endemicity to areas of low endemicity—is a key factor in increasing outbreak potential in industrialised countries.

Effective vaccines are available for the prevention of HAV, and the importance of vaccination is well established—ie, to protect those at risk from infection and reduce disease incidence by preventing transmission.^{10,11} Experiences in Italy,¹² Spain,¹³ Israel,¹⁴ and 11 states in the USA,¹¹ including American Indian and Alaska Native endemic areas,^{15,16} where universal childhood vaccination programmes against hepatitis A have been implemented, show the need for these programmes. Such strategies aim to reduce the incidence of new infections and prevent infection in adulthood, during which time clinical consequences of disease are more severe.

Lancet 2003; **362**: 1065–71

*Affiliations of consensus group members are shown in panel 1

Correspondence to: Prof Pierre Van Damme, Centre for the Evaluation of Vaccination, WHO Collaborating Centre for Control and Prevention of Viral Hepatitis, Unit of Epidemiology and Social Medicine, University of Antwerp, 2610 Antwerp, Belgium (e-mail: pierre.vandamme@ua.ac.be)

The first commercially produced HAV vaccine (Havrix, GlaxoSmithKline Biologicals, Rixensart, Belgium) was launched in 1992, followed by others shortly afterwards.¹⁷⁻¹⁹ In the 10 years since HAV vaccines became available, a substantial amount of data have been gathered on immunogenicity and long-term persistence of vaccine-induced anti-HAV antibodies.²⁰ Therefore, it is timely that we ask whether or not booster vaccination is necessary, and that booster policy is driven by the evidence available. For the purpose of this report, booster refers to vaccination some time after the manufacturers' recommended primary vaccination course.

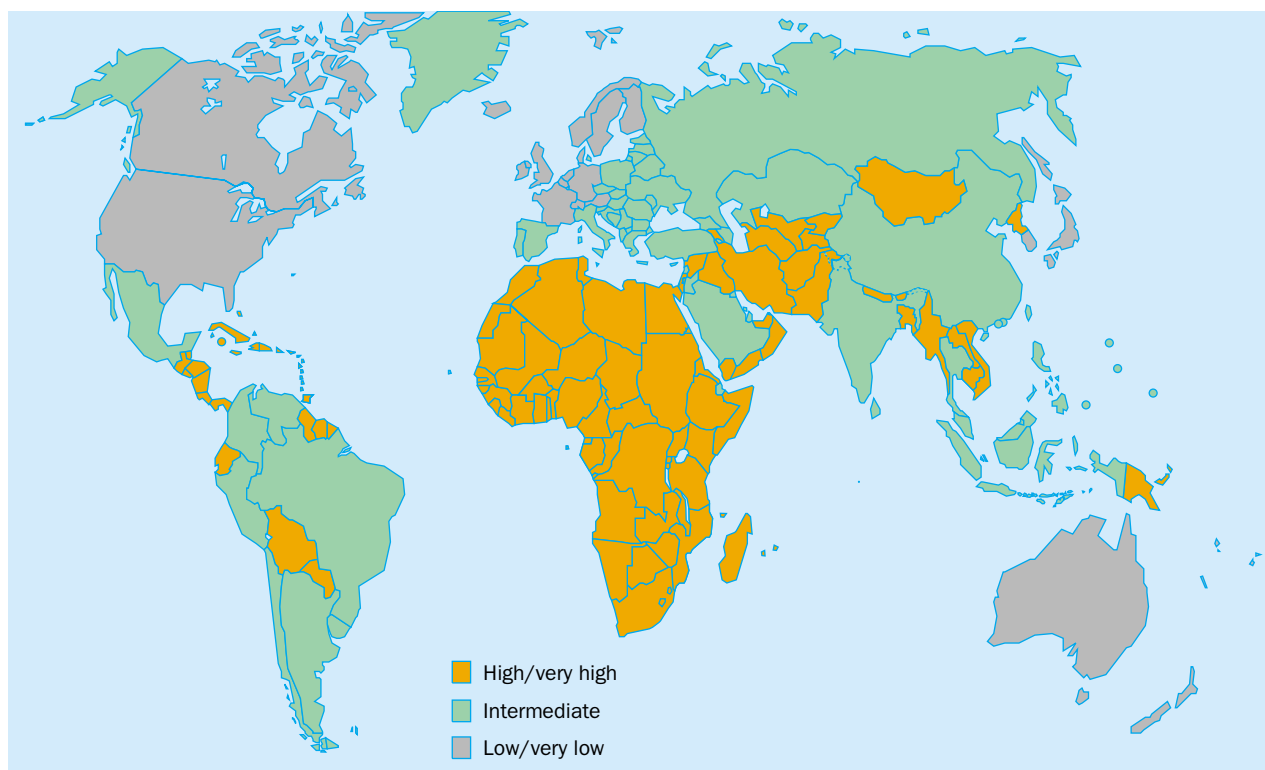
If booster vaccinations are not needed, universal vaccination of children living in areas of intermediate endemicity, as recommended by WHO, could prove more attractive, because they will acquire long-term protection extending into adulthood, when the clinical results of the disease are much more severe.⁴ Additionally, substantial cost-savings can be expected through lower vaccination costs (eg, vaccines, needles, syringes), reduced risk of disease transmission, and time saved for healthcare professionals and people receiving the vaccine.

Similarly, in 2000, a change in hepatitis B booster recommendations took place, on the basis of long-term antibody protection and evidence of the role of immune memory in providing sustained protection against hepatitis B infection.²¹ In immunocompetent individuals who have responded to a primary vaccination course, hepatitis B booster vaccinations are no longer recommended.

In June, 2002, a panel of international experts met to review the data available on the long-term immunogenicity and efficacy of HAV vaccine, including duration of protection afforded by immune memory, with the objective of providing clear guidance on whether there is a need for HAV booster vaccination.

Participant selection and search strategy

A group of international hepatitis experts was identified and invited to take part in a consensus meeting chaired by Pierre Van Damme. Participants were chosen principally on the basis of long-term hepatitis A expertise and involvement in national vaccination programmes. Every participant was invited to review published work and to present data for discussion. The consensus process and



Global pattern of hepatitis A endemicity^{4,5}

Adapted from <http://www.worldwidevaccines.com>, with permission of GlaxoSmithKline.

affiliations of participants is described in panel 1. The data search strategy included identification of review articles, original research papers, meeting reports, and editorials by searches of MEDLINE and references from relevant articles published between 1990 and 2002. Published work included data from clinical trials published since 1992, reviews of the epidemiology of HAV disease, evidence for immune memory and anamnestic response, and

current vaccination recommendations. Search terms were “adolescents”, “adults”, “anamnestic response”, “children”, “combined vaccines”, “hepatitis A”, “immune memory”, “immunocompromised”, “infants”, “travellers”, and “vaccination”. Only English language papers were reviewed. The articles for citation were chosen on the relevance of their contents without any bias towards author or journal.

Panel 1: Consensus process and affiliations of consensus group

Consensus process

The lack of any recommendations about the need for booster vaccination has presented an opportunity for experts on HAV vaccination to meet and provide guidance based on the available evidence—this was achieved by a consensus:

- Individuals recognised as thought leaders on HAV epidemiology and vaccination were identified worldwide by Pierre Van Damme.
- Panel members were asked to review current HAV vaccine recommendations for different populations and long-term antibody persistence data for HAV vaccination for every population and the evidence for longlasting immune memory.
- Findings were presented at a meeting held in June, 2002.
- The studies cited were those considered to best reflect the body of published work.
- Recommendations were developed during the meeting.
- Pierre Van Damme and Jangu Banatvala were charged with taking the output of the meeting and drafting the article presented here with contributions from the panel.

Affiliations of members

P Van Damme, Centre for the Evaluation of Vaccination, director of the WHO Collaborating Centre for Control and Prevention of Viral Hepatitis in Europe, University of Antwerp, Belgium, executive secretary to the Viral Hepatitis Prevention Board, and adviser to the Ministers of Health (regional and national); J Banatvala, former chairman of the Advisory Group on Hepatitis, UK Vaccines Advisory Committee; P Bonanni, Department of Public Health, University of Florence, Florence, Italy, and standing adviser to the Viral Hepatitis Prevention Board, regional consultant for implementation of vaccination programmes, Tuscany, Italy; B Connor, Division of Gastroenterology and Hepatology, Weill Medical College of Cornell University, and medical director, New York Center for Travel and Tropical Medicine, New York, NY, USA; G Cooksley, Royal Brisbane Hospital Research Foundation and University of Queensland, Brisbane, Australia; O Fay, Center for Technology in Public Health, WHO Reference Centre for Viral Hepatitis in Latin America, Argentina, and National Advisory Committee for Viral Hepatitis; S Iwarson, Department of Infectious Diseases, Göteborg University, Göteborg, Sweden, former adviser to the Swedish National Board of Health on vaccination issues, and chairman of the Regional Drug Selection Committee for Pricing and Reimbursement of Prescription Pharmaceuticals; G Leroux-Roels, Centre for Vaccinology, Ghent University Hospital, Ghent, Belgium; B McMahon, Viral Hepatitis Program, Alaska Native Tribal Health Consortium, Anchorage, AK, USA; D Shouval, Liver Unit, Hadassah University Hospital, Jerusalem, Israel, and standing adviser to the Viral Hepatitis Prevention Board, adviser to the Ministry of Health, Israel; K Van Herck, Centre for the Evaluation of Vaccination, WHO Collaborating Centre for Control and Prevention of Viral Hepatitis, University of Antwerp, Belgium; F Von Sonnenburg, University of Munich, Germany.

Panel 2: WHO recommendations for HAV vaccination⁴

- In highly endemic countries, almost all individuals are asymptotically infected with HAV in childhood, which effectively prevents clinical hepatitis A in adolescents and adults. In these countries, large-scale vaccination programmes are not recommended.
- In countries of intermediate endemicity where a relatively large proportion of the adult population is susceptible to HAV, and where hepatitis A represents a significant public health burden, large-scale childhood vaccination may be considered as a supplement to health education and improved sanitation.
- In regions of low endemicity, vaccination against hepatitis A is indicated for individuals with increased risk of contracting the infection, such as travellers to areas of intermediate or high endemicity.

Reprinted with permission of WHO.

Current HAV vaccination recommendations

Recommendations for primary HAV vaccination vary considerably between countries. WHO recommends that epidemiological and cost-benefit studies should be considered before deciding on national policies for HAV immunisation.⁴ The WHO recommendations for HAV vaccination are given in panel 2.

According to general recommendations, primary HAV vaccination should be administered following a two-dose schedule—with the second dose administered 6–18 months after the first dose according to the product licence—to individuals deemed at high-risk from infection, including travellers, children from immigrant families, men who have sex with men, and injecting drug users.^{11,22} Initially, the first HAV vaccine was administered according to a three-dose schedule in both children and adults. However, all vaccines are now given according to a two-dose schedule. Additionally, HAV vaccination is recommended for immunocompromised individuals, including those with blood-clotting disorders, chronic liver disease, and who are HIV-positive.^{11,22} Previously, there have been no worldwide recommendations about HAV booster policy (other than from the manufacturers or national authorities) and whether a booster is necessary to sustain longlasting protection.

Industrialised countries are generally regarded as having a low endemicity status. However, pockets of intermediate or high endemicity can be found—eg, Puglia in Italy¹² and the North Bohemian region of the Czech Republic.⁹ Thus, in some European regions, universal vaccination of children older than 1 year of age is routinely done to reduce the spread of infection in older age groups in whom clinical manifestations are more severe—eg, Puglia in Italy.

In the USA, the advisory committee on immunisation practices (ACIP) recommends universal HAV vaccination for children (aged 2–18 years) living in areas where rates of HAV are at least twice the national average—ie, where the annual HAV incidence during 1987–1997 was 20 cases or more per 100 000 population.^{11,23} Presently,

this applies to 11 US states; however, an additional six states are under consideration for inclusion in the programme. Hepatitis A is endemic in certain subpopulations in Israel, and in 1998 a programme was established to inoculate all schoolchildren.²⁴ Furthermore, as of July, 1999, HAV vaccination was started in the regular childhood vaccination programme for infants aged 18 and 24 months.¹⁴

Cellular basis of HAV immune memory

Antibody persistence has long been judged a marker for vaccine protection. However, a better understanding of immunology has led to the realisation that long-term protection is conferred by underlying immune memory. Studies to assess immune memory have examined humoral and cell-mediated responses to vaccine challenge.

Indirect evidence (humoral response)

Follow-up data in 31 adults (aged 32–40 years) show long-term persistence (12 years) of antibodies after completion of a primary HAV vaccination course.²⁵ When challenged 12 years later with half an adult booster dose of HAV vaccine, geometric mean titres rose from 242 mIU/mL at day 0 to 877 mIU/mL, 3831 mIU/mL, and 5282 mIU/mL after 7, 14, and 30 days, respectively. These data also confirm the persistence of immune memory.

Studies on HAV vaccination in adult travellers have shown that a delay in the timing of the second dose (24–72 months after the first dose) does not appear to affect the immune response (table).^{26,27} A substantial anamnestic response has been shown in 25 travellers aged 36–50 years given a booster dose 48–72 months after the first dose (geometric mean titres 32 mIU/mL and 2993 mIU/mL before and after the second dose, respectively).²⁷ Even when there is no detectable level of antibody before the booster dose, an anamnestic response is noted, indicating involvement of immune memory.^{26,27} A study in 58 Alaskan adults has also indicated that a delay in timing of the second dose (mean delay 27.2 months) does not affect the immune response (geometric mean titres 40.6 mIU/mL and 1305 mIU/mL before and after the second dose, respectively).²⁸ Although to reduce the number of doses to one HAV vaccination would be favourable, until studies show the efficacy of one dose, it is important to stress the need for full primary vaccination (preferably within the recommended period) to ensure a robust anamnestic response and long-term protection.²⁹

The data presented lend substantial support to the role of immune memory in providing sustained protection against HAV infection.

Direct evidence (cell-mediated response)

Data characterising the cellular immune response after HAV infection are rather more limited than after hepatitis B virus infection.³⁰ However, results of studies suggest that cellular immunity has an important role in the host response to HAV infection. In some patients with acute hepatitis A, production of anti-HAV antibodies is delayed without any evidence of immunodeficiency.³¹ In such

	Number of adults	Delay (months)	GMT before booster (mIU/mL)	GMT after booster (mIU/mL)
Dose type				
Delayed 2nd dose ²⁶	124	24–60	116	3342
Control ²⁶	125	0	135	3258
Delayed 2nd dose ²⁷	25	48–77	32	2993
Delayed 2nd dose ²⁸	58	20–31	211	1547

GMT=geometric mean titre.

Immune response in adults after delayed second dose of HAV vaccine

cases, evidence for an immune response has been indicated by the activation of the interferon system before the appearance of specific antibodies.

Studies in chimpanzees provided early evidence of immune memory to HAV post-vaccination. When chimpanzees were immunised with formalin-inactivated HAV antigen, they were protected against challenge with infectious HAV, even in the absence of detectable amounts of anti-HAV antibody.³² These data indicate that detectable levels of anti-HAV antibodies are not an absolute requirement for protective immunity.

Results of early cellular immunity studies with spot ELISA techniques in 63 individuals showed that HAV vaccine can generate memory B-cells producing IgG anti-HAV 1.5–2 years after primary vaccination.³³ Furthermore, a T-cell response is seen 2–3 years after primary vaccination (shown by lymphocyte proliferation and T-cell activation to HAV *in vitro*). The T-cell mediated response is thought to have an important role in long-term protection after natural HAV infection and after HAV vaccination.³⁴ Cederna and colleagues assessed humoral and proliferative T-cell responses after HAV vaccine administration in ten individuals.³⁵ Data suggested that inactivated HAV vaccine resulted in an early proliferative T-cell response in seven of the ten by week 10, and in all individuals by week 30, which lasted for at least 5 months and was accompanied by production of interferon γ .³⁵ The role of T-cell immune memory in long-term protection against HAV infection has been examined 72 months after primary vaccination in adults (n=36).³⁶ Those with a high anti-HAV titre (>200 IU/L) at month 60 showed a more robust cell-mediated immune response with significantly higher amounts of HAV-induced interferon γ secretion ($p < 0.005$) than those with a low antibody titre (<200 IU/L) at month 60. Persistent anti-HAV antibody levels are not necessary for sustained protection; however, initially high anti-HAV levels could indicate a strong T-cell response, a theory that remains to be confirmed.

Immunogenicity of primary hepatitis A vaccination in different populations

The protective efficacy of a primary course of HAV vaccine has been established by many studies of vaccinated populations.^{37,38} Before 1995, one type of HAV vaccine (Havrix) was administered according to a three-dose schedule; therefore, a large number of the studies presented here relate to the three-dose vaccination course rather than the now universally accepted two-dose schedule. After presentation of the data available for long-term antibody protection, comment will be made on the reliability of underlying immune memory for every population.

Infants, up to 2 years of age

In Europe, HAV vaccination is administered after a two-dose schedule to individuals older than age 12 months. In the USA, the starting age for HAV vaccination is 2 years of age, because the ACIP have raised concerns about the appropriate dose and timing of vaccination in young children.¹¹ Concern was expressed that presence of maternal antibodies interfered with seroconversion and induction of immune memory.³⁹

The immunogenicity and safety of HAV vaccine in children younger than 2 years of age has been studied. In infants from HAV-negative mothers, a high seroconversion rate (100%) is noted after HAV vaccination.^{40–42} Infants with maternal antibodies to HAV virus also had a high seroconversion rate (93–100%) after completion of the primary vaccination.^{41–43} Importantly,

although the presence of maternal antibodies is associated with lower geometric mean titres than those in children from anti-HAV-negative mothers, the anamnestic response, when challenged by booster vaccination, is robust, even 6 years post-vaccination.^{41,44} The high anti-HAV antibody levels seen after primary vaccination, together with evidence of a robust anamnestic response after booster vaccination, suggest there is no support for booster vaccination in this population.

Children and adolescents

The potential benefits of universal childhood vaccination in areas of intermediate endemicity are increasingly well documented.^{12,45,46} Mass primary vaccination of children and adolescents aged between 2–18 years will lower the incidence of HAV among adults—eg, Israel and Slovakia.^{14,47}

High seroconversion rates have been achieved in children (n=96) receiving a three-dose schedule (0, 1, and 6 months) of HAV vaccine, with 100% seropositivity at 7 months.⁴⁸ The highest geometric mean titres (4133 mIU/mL) of anti-HAV were seen at 7 months and declined throughout the follow-up period (403 mIU/mL at 60 months). However, long-term follow-up data show 100% seropositivity in children at 60 months. Another study initiated in children aged 1–6.8 years (n=107) showed similar results, with 100% seropositivity at 7 months.⁴⁹ The geometric mean titres peaked at month 7 (3802 mIU/mL) and declined until the end of follow-up at month 60 (661 mIU/mL). All individuals remained seropositive at month 60.

A study of a two-dose schedule of HAV vaccination in Alaskan children has shown that a delay in timing of the second dose (mean delay 27 months) does not affect the immune response. After the delayed second dose, 157 participants, 79 of whom were 19 years of age or younger, were tested for anti-HAV antibodies. All responded to the second dose, even though no detectable level of antibodies was detected before the second dose in 17% of participants, indicating an underlying immune memory.²⁸

Mathematical models based on the three-dose primary vaccination schedule (360 ELISA units) predicted between 14 and 20 years of antibody persistence,^{48,49} and underlying immune memory can be expected to persist well beyond this time, suggesting there is no need for booster vaccination in this population. The accepted two-dose vaccination schedule (720 ELISA units) also provides a robust immunological priming.⁵⁰ Results of additional studies in children, with a different hepatitis A vaccine, have shown that after completion of a primary vaccination course, anti-HAV antibodies can be detected 6–9 years after last dose.^{51–53} Long-term persistence of antibodies is predicted to last at least 30 years.⁵²

Adults

Infection in adulthood is generally associated with severe clinical manifestations, and recommendations of the ACIP and WHO for adult immunisation against hepatitis A in countries of low endemicity are indicated for those judged at high-risk from infection—eg, travellers to countries of intermediate or high endemicity, children from immigrant families, men who have sex with men, and illegal drug users—and those with pre-existing medical disorders such as haemophilia.^{4,11}

High anti-HAV antibody levels and seroconversion rates are noted in adults after administration of a primary vaccination course, even with a delay in the timing of

the second dose.^{26,27,54–56} Follow-up data in adults show long-term persistence (12 years) of anti-HAV antibodies after primary vaccination with a three-dose (0, 1, and 6 months) HAV vaccine (geometric mean titre 242 mIU/mL).²⁵ Mathematical models estimate the long-term persistence of anti-HAV antibodies to be more than 25 years.⁵⁷

The high anti-HAV antibody amounts seen in immunocompetent adults combined with the projected times for antibody persistence and the evidence of immune memory involvement do not lend support to the need for booster vaccination in this population.

Special patient-groups

Throughout the industrialised world, a general recommendation is that individuals with chronic liver disease, clotting-factor disorders, and people who are HIV positive should be vaccinated against HAV infection because of the potential for enhanced risk of infection or severe disease.^{7,11,22}

Individuals with chronic liver disease might include susceptible people awaiting or who have received a liver transplant, those with chronic hepatitis B or C virus, and individuals with alcoholic liver disease. HAV vaccine was well tolerated in 475 adults (older than 18 years of age) with either chronic liver disease, chronic hepatitis B virus infection, or chronic hepatitis C virus infection.⁵⁸ After the second dose, more than 94% of individuals were seropositive for anti-HAV. However, at month 7, reduced geometric mean titres were seen compared with those obtained for healthy individuals (chronic liver disease 562 mIU/mL, hepatitis B virus 749 mIU/mL, hepatitis C virus 467 mIU/mL, and healthy individuals 1315 mIU/mL).⁵⁸ In another study in 60 adults (aged 17–47 years) with chronic liver disease, 100% seroconversion was reported after primary vaccination at month 7, with a geometric mean titre of 1309 mIU/mL.⁵⁹

After completion of a two-dose vaccination schedule, a lower seroconversion rate was recorded in 90 HIV-positive men than in 44 HIV-negative individuals (88.2% and 100%, respectively).⁶⁰ Furthermore, antibody values were also lower in HIV-positive men (geometric mean titres 101 IU/L vs 1086 IU/L). The success of seroconversion in HIV-positive individuals was related to their CD4+ count.

In general, although lower seroconversion rates and lower antibody concentrations were reported in HIV-positive individuals and in those with chronic liver disease than in healthy individuals, protection against HAV infection in these special patient-groups can be achieved. Studies on the persistence of antibodies are needed, and will allow recommendations on booster vaccination to be developed in this population.

Equivalent efficacy of HAV vaccine after administration as a combined vaccine

The addition of HAV vaccination into extended programmes of vaccination that already include hepatitis B virus vaccination—eg, Puglia in Italy, Catalonia in Spain—provide an ideal situation for use of a combined vaccine in terms of cost-effectiveness, higher compliance, and convenience.¹² Therefore, the issue of booster vaccination must be examined in the context of combination vaccines.

Combined vaccines—eg, against HAV and hepatitis B virus, HAV and typhoid—are also available for use in travellers and other indicated population groups.^{10,12,61–63} As combined vaccines are increasingly used, it is important that they result in an equivalent HAV immune response to

that induced by monovalent vaccines. Available data suggest the immunogenicity of a combined HAV and hepatitis B virus vaccine is comparable with that of the monovalent vaccines.^{64–66}

Long-term persistence of anti-HAV and anti-HBs antibodies has been recorded in children and adults immunised with a combined hepatitis A and B vaccine after 60 and 72 months, respectively.⁶³ Throughout the follow-up period, all individuals remained seropositive for HAV, and more than 89% had anti-HBs titres that remained above 10 mIU/mL.

A single-dose combined vaccine against hepatitis A and typhoid fever has been shown to be highly immunogenic in 462 individuals aged 15–50 years.⁶² At month 1, seropositivity rates for anti-typhoid and anti-HAV antibodies were 95.7% (geometric mean titre 1023 mIU/mL) and 99% (geometric mean titre 452 mIU/mL), respectively. 1 month after the second dose of HAV vaccine given at month 6, the anti-HAV antibody amount rose (geometric mean titre 3392 mIU/mL) and all individuals were seropositive.

The immunological response against hepatitis A obtained with a combined vaccine shows no support exists for HAV booster when a combined hepatitis A and B vaccine, or a combined hepatitis A and typhoid vaccine, is used for the primary vaccination course. However, new hepatitis A combined vaccines should be assessed for equivalent immunogenicity to the monovalent vaccine.

Conclusions

If HAV booster vaccinations are not needed, because of the long-term protection provided by primary HAV vaccination, then universal vaccination of children living in areas of intermediate endemicity might prove more attractive. Not only will this strategy provide long-term protection against hepatitis A extending into adulthood but also it will result in substantial cost-savings through lower vaccination costs.

Available data show that HAV vaccines provide longlasting protection in immunocompetent individuals. Evidence of immunity, in the form of persisting anti-HAV antibodies, an anamnestic response to a vaccine challenge, or both, has been shown in adults up to 12 years after receiving a full course of HAV vaccine. Furthermore, mathematical models predict antibody levels will persist beyond 25 years in immunocompetent adults. For children, long-term antibody persistence has been noted up to 6 years post vaccination, and mathematical modelling lends support to persistence of antibody for 14 years. For infants (younger than 1 year of age), irrespective of the presence of maternal antibodies, immune memory is induced, and an anamnestic response has been shown 6 years post vaccination.

Thus, evidence is accumulating to show that HAV vaccine elicits immune memory that persists even after loss of detectable antibody. We recommend that reliance be placed on immunological memory rather than booster doses to protect against symptomatic infection.

We recommend that long-term studies continue in vaccinated infants, children, and adults to monitor the duration of protection afforded by immune memory. Further studies are needed to compare the immune response after naturally acquired infection and vaccination. We also recommend long-term studies in special patient-groups, including immunocompromised patients and those with chronic liver disease, be undertaken. Furthermore, we recommend continued surveillance to monitor long-term efficacy.

The recommended schedules for HAV vaccines consist of a complete primary course, as described in the product license. Results of preliminary studies show that even one dose induces long-term immune memory. Therefore, the primary course can be continued without restarting, even after an extended interval before the second dose. Additional studies are needed to explore the long-term efficacy of a single dose. To date, no data lend support to the need for booster doses of HAV vaccine in immunocompetent individuals who have received a full vaccination course.

Contributors

Based on the presentations and discussions held at the meeting in June, 2002, including wording of the consensus statement, P Van Damme and J Banatvala drafted a consensus paper. All participants of the meeting (P Van Damme, J Banatvala, O Fay, S Iwarson, B McMahon, K Van Herck, D Shouval, P Bonanni, B Connor, G Cooksley, G Leroux-Roels, F Von Sonnenburg) made writing and editorial contributions to the final version presented here.

Conflict of interest statement

As experts in the area, many authors were principal investigators in vaccine trials and acted as advisers to pharmaceutical companies, government authorities, and charitable organisations. The chairman of the group, PVD, has done vaccine trials for several vaccine manufacturers, and is presently involved in a research project funded by the European Commission (Fifth Framework programme) for a feasibility study of surveillance and control of hepatitis A and B.

Acknowledgments

GlaxoSmithKline Biologicals (Rixensart, Belgium) provided an unrestricted educational grant towards the organisation of this consensus meeting. The funding source had no involvement on the choice of experts, the writing of the consensus, or in the decision to submit the paper for publication.

References

- 1 Hadler S. Global impact of hepatitis A virus infection: changing patterns. In: Margolis H, ed. *Viral hepatitis and liver disease*. Baltimore: Williams and Wilkins, 1991: 14–20.
- 2 Koff RS. Hepatitis A. *Lancet* 1998; **351**: 1643–49.
- 3 Webster G, Barnes E, Dusheiko G, Franklin I. Protecting travellers from hepatitis A. *BMJ* 2001; **322**: 1194–95.
- 4 WHO. WHO position paper on hepatitis A vaccines. *Wkly Epidemiol Rec* 2000; **75**: 38–44.
- 5 GlaxoSmithKline. Hepatitis A epidemiology. http://www.worldwidevaccines.com/hepatitis_a/epidemiology.asp (accessed April 11, 2003).
- 6 Nordenfelt E. Current epidemiological trends of viral hepatitis in northern Europe. In: Verme G, ed. *Viral hepatitis and liver disease*. Turin: Edizioni Minerva Medica, 1997: 545–50.
- 7 Crowcroft NS, Walsh B, Davison KL, Gungabissoon U. Guidelines for the control of hepatitis A virus infection. *Commun Dis Public Health* 2001; **4**: 213–27.
- 8 Zanetti A. Changing patterns of viral hepatitis in Southern Europe. In: Verme G, ed. *Viral hepatitis and liver disease*. Turin: Edizioni Minerva Medica, 1997: 551–54.
- 9 Beran J, Douda P, Rychly R. Seroprevalence of viral hepatitis A in the Czech Republic. *Eur J Epidemiol* 1999; **15**: 805–08.
- 10 Loscher T, Keystone JS, Steffen R. Vaccination of travelers against hepatitis A and B. *J Travel Med* 1999; **6**: 107–14.
- 11 ACIP. Prevention of hepatitis A through active or passive immunization: recommendations of the advisory committee on immunization practices (ACIP). *MMWR Morb Mortal Wkly Rep* 1999; **48**: 1–37.
- 12 Lopalco PL, Salleras L, Barbuti S, et al. Hepatitis A and B in children and adolescents: what can we learn from Puglia (Italy) and Catalonia (Spain)? *Vaccine* 2000; **19**: 470–74.
- 13 Salleras L, Bruguera M, Buti M, Domingez A. Prospects for vaccination against hepatitis A and B in Catalonia (Spain). *Vaccine* 2000; **18** (Suppl): 80–82.
- 14 Dagan R. The first national program of vaccination against hepatitis A virus (HAV): the Israel experiment. Proceedings of the 20th annual meeting of the European Society for Paediatric Infectious Diseases (ESPID); 2002 May 29–31; Vilnius, Lithuania. European Society for Paediatric Infectious Diseases, 2002: 14.
- 15 Bulkow LR, Wainwright RB, McMahon BJ, et al. Secular trends in hepatitis A virus infection among Alaska Natives. *J Infect Dis* 1993; **168**: 1017–20.

- 16 Shaw FE Jr, Shapiro CN, Welty TK, Dill W, Reddington J, Hadler SC. Hepatitis transmission among the Sioux Indians of South Dakota. *Am J Public Health* 1990; **80**: 1091–94.
- 17 Nalin DR, Kuter BJ, Brown L, et al. Worldwide experience with the CR326F-derived inactivated hepatitis A virus vaccine in pediatric and adult populations: an overview. *J Hepatol* 1993; **18** (suppl): 51–55.
- 18 Loutan L, Bovier P, Althaus B, Gluck R. Inactivated virosome hepatitis A vaccine. *Lancet* 1994; **343**: 322–24.
- 19 Dagan R, Greenberg D, Goldenberg-Gehtman P, et al. Safety and immunogenicity of a new formulation of an inactivated hepatitis A vaccine. *Vaccine* 1999; **17**: 1919–25.
- 20 Andre F, Damme P Van, Safary A, Banatvala J. Inactivated hepatitis A vaccine: immunogenicity, efficacy, safety and review of official recommendations for use. *Expert Rev Vaccines* 2002; **1**: 9–23.
- 21 European Consensus Group on Hepatitis B Immunity. Are booster immunisations needed for lifelong hepatitis B immunity? *Lancet* 2000; **355**: 561–65.
- 22 VHPB. Current recommendations on HAV control in selected countries in Europe. *Viral Hepatitis* 1999; **8**: 12–13.
- 23 ACIP. Recommended childhood immunization schedule: United States. *MMWR Morb Mortal Wkly Rep* 2001; **50**: 7–10, 19.
- 24 Fishman RHB. Hepatitis A vaccine for Israeli children. *Lancet* 1998; **352**: 888.
- 25 Van Damme P, Van Herck K. Hepatitis A vaccination: more convenience for the traveller? Proceedings of the 3rd European Conference on Travel Medicine; 2002 May 15–18; Florence, Italy. Rimini: World Health Organization Collaborating Centre for Travel Medicine, 2002: 50 (abstr 31).
- 26 Landry P, Tremblay S, Darioli R, Genton B. Inactivated hepatitis A vaccine booster given \geq 24 months after the primary dose. *Vaccine* 2000; **19**: 399–402.
- 27 Iwarson S, Lindh M, Widerstrom L. Excellent booster response 4–6 y after a single primary dose of an inactivated hepatitis A vaccine. *Scand J Infect Dis* 2002; **34**: 110–11.
- 28 Williams J, Bruden D, McMahon B, et al. Response to two doses of hepatitis A vaccine administered an average of 27 months apart. *Antiviral Ther* 2000; **13**: 5.
- 29 Iwarson S. Are we giving too many doses of hepatitis A and B vaccines? *Vaccine* 2002; **20**: 2017–18.
- 30 Banatvala J, Damme P Van, Oehen S. Lifelong protection against hepatitis B: the role of vaccine immunogenicity in immune memory. *Vaccine* 2000; **19**: 877–85.
- 31 Zachoval R, Kroener M, Brommer M, Deinhardt F. Serology and interferon production during the early phase of acute hepatitis A. *J Infect Dis* 1990; **161**: 353–54.
- 32 Purcell RH, D’Hondt E, Bradbury R, et al. Inactivated hepatitis A vaccine: active and passive immunoprophylaxis in chimpanzees. *Vaccine* 1992; **10** (suppl): 148–51.
- 33 Chen X. The immune response to hepatitis A vaccination: studies in vivo and in vitro. Utrecht: University Hospital Utrecht, 1996.
- 34 Lemon SM. Immunologic approaches to assessing the response to inactivated hepatitis A vaccine. *J Hepatol* 1993; **18** (Suppl): 15–19.
- 35 Cederna JB, Klinzman D, Stapleton JT. Hepatitis A virus-specific humoral and cellular immune responses following immunization with a formalin-inactivated hepatitis A vaccine. *Vaccine* 2000; **18**: 892–98.
- 36 Leroux-Roels G, Desombere I, Van Herck K, Thoelen S, Collard F, Van Damme P. Long-term persistence of cellular immunity towards hepatitis A virus following hepatitis A virus vaccination. In: Dienstag J, ed. *Viral hepatitis and liver diseases*. Proceedings of the 10th International Symposium on Viral Hepatitis and Liver Diseases; April 9–13, 2000; Atlanta, USA; Atlanta: International Medical Press, 2002: 41–44.
- 37 Werzberger A, Mensch B, Kuter B, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. *N Engl J Med* 1992; **327**: 453–57.
- 38 Innis BL, Snitbhan R, Kunasol P, et al. Protection against hepatitis A by an inactivated vaccine. *JAMA* 1994; **271**: 1328–34.
- 39 Kanra G, Yalcin SS, Ceyhan M, Yurdakok K. Clinical trial to evaluate immunogenicity and safety of inactivated hepatitis A vaccination starting at 2-month-old children. *Turk J Pediatr* 2000; **42**: 105–08.
- 40 Troisi CL, Hollinger FB, Krause DS, Pickering LK. Immunization of seronegative infants with hepatitis A vaccine (HAVRIX; SKB): a comparative study of two dosing schedules. *Vaccine* 1997; **15**: 1613–17.
- 41 Dagan R, Amir J, Mijalovsky A, et al. Immunization against hepatitis A in the first year of life: priming despite the presence of maternal antibody. *Pediatr Infect Dis J* 2000; **19**: 1045–52.
- 42 Piazza M, Safary A, Vegnente A, et al. Safety and immunogenicity of hepatitis A vaccine in infants: a candidate for inclusion in the childhood vaccination programme. *Vaccine* 1999; **17**: 585–88.
- 43 Abarca K, Ibanez I, Flores J, et al. Efficacy of hepatitis A vaccination in children aged 12 to 24 months. *Arch Med Res* 2001; **32**: 468–72.

- 44 Fiore AE, Shapiro C, Sabin KM, Labonte K, Bell BP, Margolis HS. Persistence of protective antibody concentrations and response to a booster among children given hepatitis A vaccine during infancy: effect of maternal antibody. Proceedings of the 39th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2001 Oct 25–28; San Francisco, USA. San Francisco: Infectious Diseases Society of America, 2001: 378.
- 45 Koff RS. The case for routine childhood vaccination against hepatitis A. *N Engl J Med* 1999; **340**: 644–45.
- 46 Ginsberg GM, Slater PE, Shouval D. Cost-benefit analysis of a nationwide infant immunization programme against hepatitis A in an area of intermediate endemicity. *J Hepatol* 2001; **34**: 92–99.
- 47 Prikazsky V, Olear V, Cernoch A, et al. Interruption of an outbreak of hepatitis A in two villages by vaccination. *J Med Virol* 1994; **44**: 457–59.
- 48 Chan CY, Lee SD, Yu MI, et al. Long-term follow-up of hepatitis A vaccination in children. *Vaccine* 1999; **17**: 369–72.
- 49 Fan PC, Chang MH, Lee PI, et al. Follow-up immunogenicity of an inactivated hepatitis A virus vaccine in healthy children: results after 5 years. *Vaccine* 1998; **16**: 232–35.
- 50 Findor JA, Canero Velasco MC, Mutti J, Safary A. Response to hepatitis A vaccine in children after a single dose with a booster administration 6 months later. *J Travel Med* 1996; **3**: 156–59.
- 51 Werzberger A, Kuter B, Nalin D. Six years' follow-up after hepatitis A vaccination. *N Engl J Med* 1998; **338**: 1160.
- 52 Wiens BL, Bohidar NR, Pigeon JG, et al. Duration of protection from clinical hepatitis A disease after vaccination with VAQTA. *J Med Virol* 1996; **49**: 235–41.
- 53 Werzberger A, Mensch B, Nalin DR, Kuter BJ. Effectiveness of hepatitis A vaccine in a former frequently affected community: 9 years' followup after the Monroe field trial of VAQTA. *Vaccine* 2002; **20**: 1699–701.
- 54 Damme P Van, Mathei C, Thoelen S, et al. Single dose inactivated hepatitis A vaccine: rationale and clinical assessment of the safety and immunogenicity. *J Med Virol* 1994; **44**: 435–41.
- 55 Briem H, Safary A. Immunogenicity and safety in adults of hepatitis A virus vaccine administered as a single dose with a booster 6 months later. *J Med Virol* 1994; **44**: 443–45.
- 56 Herck K Van, Damme P Van. Inactivated hepatitis A vaccine-induced antibodies: follow-up and estimates of long-term persistence. *J Med Virol* 2001; **63**: 1–7.
- 57 Van Herck K, Renard D, Molenberghs G, Van Damme P. Model-based estimates of long-term persistence of vaccine induced hepatitis A antibodies. In: Dienstag J, ed. *Viral hepatitis and liver diseases*. Proceedings of the 10th International Symposium on Viral Hepatitis and Liver Diseases; 2000 April 9–13; Atlanta, USA. Atlanta: International Medical Press, 2002: 56–59.
- 58 Keeffe EB, Iwarson S, McMahon BJ, et al. Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease. *Hepatology* 1998; **27**: 881–86.
- 59 Lee SD, Chan CY, Yu MI, et al. Safety and immunogenicity of inactivated hepatitis A vaccine in patients with chronic liver disease. *J Med Virol* 1997; **52**: 215–18.
- 60 Neilsen GA, Bodsworth NJ, Watts N. Response to hepatitis A vaccination in human immunodeficiency virus-infected and -uninfected homosexual men. *J Infect Dis* 1997; **176**: 1064–67.
- 61 Damme P Van, Wielen M Van der. Combining hepatitis A and B vaccination in children and adolescents. *Vaccine* 2001; **19**: 2407–12.
- 62 Beran J, Beutels M, Levie K, et al. A single dose, combined vaccine against typhoid fever and hepatitis A: consistency, immunogenicity and reactogenicity. *J Travel Med* 2000; **7**: 246–52.
- 63 Damme P Van, Leroux-Roels G, Law B, et al. Long-term persistence of antibodies induced by vaccination and safety follow-up, with the first combined vaccine against hepatitis A and B in children and adults. *J Med Virol* 2001; **65**: 6–13.
- 64 Joines RW, Blatter M, Abraham B, et al. A prospective, randomized, comparative US trial of a combination hepatitis A and B vaccine (Twinrix) with corresponding monovalent vaccines (Havrix and Engerix-B) in adults. *Vaccine* 2001; **19**: 4710–19.
- 65 Kallinowski B, Knoll A, Lindner E, et al. Can monovalent hepatitis A and B vaccines be replaced by a combined hepatitis A/B vaccine during the primary immunization course? *Vaccine* 2000; **19**: 16–22.
- 66 Thoelen S, Damme P Van, Leentvaar-Kuypers A, et al. The first combined vaccine against hepatitis A and B: an overview. *Vaccine* 1999; **17**: 1657–62.